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# A DOG MODEL OF FULMINANT HEPATIC FAILURE PRODUCED BY PARACETAMOL ADMINISTRATION

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**Summary.—Oral administration of graded doses of paracetamol to dogs produced hepatic necrosis with some similarities to the clinical syndrome seen in man following a paracetamol overdose. Coma, with raised levels of arterial ammonia, was produced and the aspartate aminotransferase levels became markedly elevated in 2 animals who survived more than 24 h. However, the extent of the hepatic necrosis and the time of survival following paracetamol administration were too variable for this model to be of value for the testing of new methods of temporary liver support. When paracetamol was given by intraperitoneal injection many of the animals died of respiratory distress. Significant methaemoglobinaemia was detected, which was associated with a reduction in the arterial partial pressure of oxygen and was partly reversed by the administration of methylene blue.**

THERE IS a reluctance to evaluate new treatments of fulminant hepatic failure by means of controlled trials because of the high mortality and the many factors affecting the outcome. Prior testing in an animal model would be of assistance but the hepatic necrosis induced must be easily reproduced and ideally should cause an illness similar to that seen in man. In many of the currently used models, necrosis is induced by graded hepatic ischaemia after portacaval shunt (Rappaport, McDonald and Borowy, 1953) but this is an irreversible process whereas in man there is, at least in a number of cases, potential for recovery.

One of the commoner causes of fulminant hepatic failure in man is overdosage with paracetamol (Prescott *et al.*, 1971) and in animals this drug is a dose-dependant hepatotoxin (Dixon, Nimmo and Prescott, 1971)

The possibility of being able to produce an animal model in this way prompted the present studies, in which paracetamol was administered to the dog in different doses *via* oral and peritoneal routes. The dog was chosen since it is a sufficiently large animal for trying out new techniques of artificial liver support.

## MATERIALS AND METHODS

Greyhound dogs (18–30 kg body weight) were anaesthetized using Pentothal and then intubated using a cuffed endotracheal tube. The duration of anaesthesia was short, all animals recovering consciousness within 1 h. During this time a graded dose of a paracetamol suspension was administered orally *via* a wide-bore tube inserted in the stomach, or by intraperitoneal injection. In addition, all the dogs were given an intramuscular injection of cloxacillin (500 mg) and gentamicin (80 mg). Subsequently the animals received intravenous 10% dextrose (500 ml) every 4 h to prevent hypoglycaemia.

Repeated blood samples were obtained from an indwelling venous catheter and arterial line. Serum bilirubin and plasma aspartate aminotransferase levels were measured on an SMA-12 machine, arterial blood ammonia by the method of Kirsten, Gerez and Kirsten (1963) and levels of plasma unconjugated paracetamol by an ether extraction method (Dordoni *et al.*, 1973). The presence of methaemoglobin was also determined in those animals given an intraperitoneal injection of paracetamol (Evelyn and Malloy, 1938). Histological evaluation of the hepatic necrosis was obtained at autopsy which was performed shortly after death, those dogs which recovered being killed at 5 days. Liver

TABLE.—*Survival Time, Liver Histology and Maximum Biochemical Abnormalities Occurring in the 6 Dogs given an Oral Paracetamol Suspension (1 g/kg body weight)*

| Dog | Survival time (h) | Plasma ammonia (μmol/l | Serum bilirubin (μmol/l) | Serum aspartate aminotransferase (iu/l) | Liver histology |
|---|---|---|---|---|---|
| 1 | 36 | 340 | 170 | 2500 | Extensive necrosis |
| 2 | 26 | 155 | 42 | 8000 | Congestion only |
| 3 | 12 | 257 | 19 | 1350 | Congestion and fatty change |
| 4 | 27 | 320 | 19 | 1425 | Fine fat vacuoles |
| 5 | 10 | — | 15 | 106 | Normal |
| 6 | 8 | — | 19 | 65 | Normal |

sections were stained with haematoxylin and eosin after fixation in formol saline.

## RESULTS

The 3 dogs given paracetamol orally in a dose of 3 g/kg body weight became unconscious and cyanosed within 3 h of recovery from the anaesthetic and died 6, 8 and 12 h afterwards. All 6 dogs in the group given a lower dose of 1 g/kg body weight became unconscious within 4 h of recovery from anaesthesia. Three of them died 8, 10 and 12 h after administration of the paracetamol, while the other 3 animals recovered consciousness after 7 to 10 h but lapsed into coma again 21 to 31 h later and died (Table). All the animals had abnormalities of liver function, with raised levels of aspartate aminotransferase and arterial ammonia. In 2 animals the serum bilirubin level was also increased. These changes were noted within 6 h of paracetamol administration and became most marked in 2 animals surviving more than 24 h. Only one of the 6 animals had extensive hepatic necrosis at autopsy. The others showed minor abnormalities only.

The plasma unconjugated paracetamol levels rose to a peak within 1 h of ingestion, followed by a plateau over the next 12 h (Fig. 1). There was no correlation between the plasma paracetamol levels and the severity of the changes in liver function.

### *Intraperitoneal administration*

The 2 animals given the lower doses of paracetamol (0·25 and 0·5 g/kg body weight) by intraperitoneal injection showed

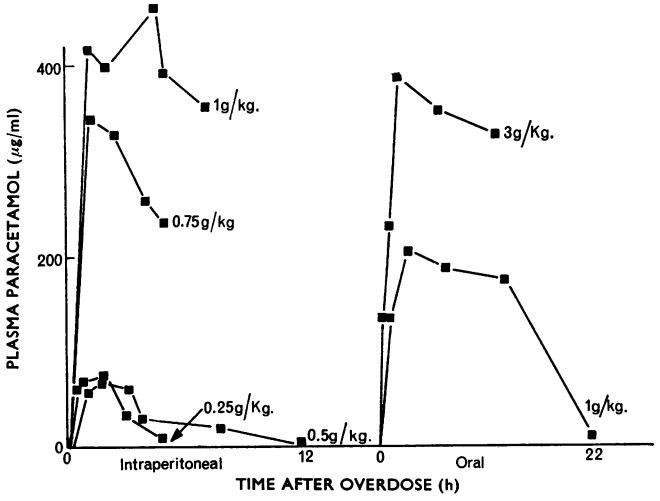


FIG. 1.—Plasma paracetamol levels following oral and intraperitoneal administration of the drug. The mean values for the 6 dogs given 1 g/kg body weight orally are shown.

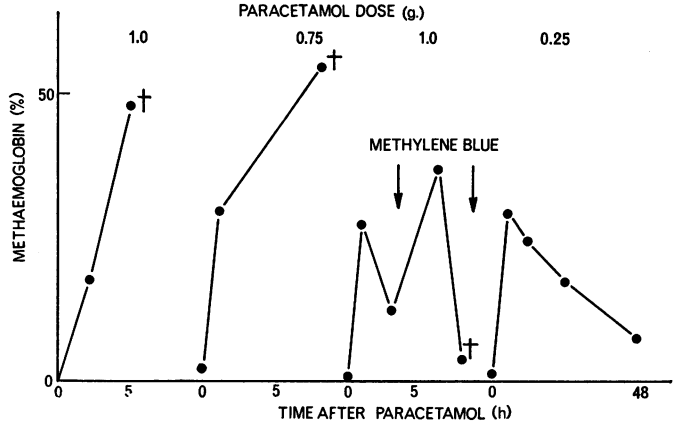


FIG. 2.—Methaemoglobin levels in 4 animlas expressed as a percentage of the total haemoglobin concentration. The administration of methylene blue to one animal is indicated by the arrows.

no change in conscious level and no evidence of liver damage at autopsy, whereas those given higher dosages (0·75 g/kg to one animal and 1 g/kg to 2 animals) became unconscious and cyanosed within 2 h of recovering from the anaesthetic. Partial pressures of oxygen in arterial blood samples at this time were less than 5 kPa. Methaemoglobinaemia was detected in the 4 dogs in whom this was measured (Fig. 2) and the 2 animals in which this formed more than 40% of the total haemoglobin died rapidly. Those developing less extensive methaemoglobinaemia had been given the lower doses of paracetamol and recovered. The effect of methylene blue was tried in one of the dogs in which 25% of the haemoglobin was present as methaemoglobin at 1 h. It was administered in a dose of 1 mg/kg body weight and following this the percentage of methaemoglobin fell and the arterial $pO_2$ rose from 5 to 7 kPa (Fig. 2). The effect was, however, short-lived and despite another dose 3 h later, the animal died 12 h after the administration of paracetamol.

There was a more rapid rise in the plasma levels of unconjugated paracetamol in the animals given an intraperitoneal injection than in the group given the drug orally (Fig. 1).

## DISCUSSION

There were certain similarities between the liver damage developing in some of these animals and the clinical picture seen in man following a paracetamol overdose. Coma, with raised levels of arterial ammonia, certainly occurred and evidence of hepatic damage became most marked after 24 h, as in man. However, this model would clearly be of little value as a system for testing new treatments for fulminant hepatic failure as the degree of hepatic damage and survival time were too variable. Paracetamol induced liver damage in the rat is potentiated by the prior administration of phenobarbitone to induce the hepatic microsomal enzymes (Mitchell *et al.*, 1973*b*) and it is possible that the same would also occur in the dog. However, other workers who have attempted to produce a similar model in the pig by administering paracetamol, with and without hepatic enzyme induction, have noticed a similar variability in survival time (Terblanche *et al.*, 1975).

Many of the dogs given the larger doses of paracetamol died rapidly, apparently of respiratory failure, at a time when there were only mild disturbances of liver function. Measurements in the animals given the drug by the intraperitoneal route showed marked methaemoglobinaemia,

and it is possible that this was also the cause of the respiratory distress in those animals given the drug orally. Methaemoglobinaemia has been reported in the cat following paracetamol administration (McLean *et al.*, 1967) but does not apparently occur in man. One of the mechanisms normally preventing the formation of methaemoglobin is the presence within the red cell of reduced glutathione, and the administration of paracetamol may have led to a lowered concentration of this. Mitchell *et al.* (1973*a*) have shown that hepatic levels of glutathione are reduced in the mouse following paracetamol overdosage and there is some evidence that red blood cell and liver stores of this compound are interchangeable (Elwyn, Parikh and Shoemaker, 1968). The use of methylene blue as a reducing agent, which has been used as a treatment for methaemoglobinaemia, had only a transient effect in the one animal studied. Unfortunately, it seems that a dose of paracetamol sufficient to cause a reproducible syndrome of hepatic necrosis in the dog cannot be given without the occurrence of methaemoglobinaemia and death from respiratory distress.

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